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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,876	06/08/2006	Roy Larsen	50147/010001	9168

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
09/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/552,876	LARSEN ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "**said**," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Objections

2. Claim 19 is objected to because of the following informalities: The instant claim does not end in a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-7 and 9-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the diseases listed in the instant claim 8, does not reasonably provide enablement for all soft tissue disease. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to utilize the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1. The nature of the invention, state of the prior art, relative skill of those in the art, and the predictability of the art

The claimed invention relates to the method for the treatment of soft tissue disease in a mammalian subject, which encompasses any soft tissue disease. Various soft tissue diseases having various different causes are not treatable by a single composition. Given the great diversity between various soft tissue diseases (bacterial infection, heart disease, neurological diseases, etc.), the unpredictability of treating an animal (e.g., no specific soft tissue disease) has a number of facets, as discussed hereinafter.

A. Treatment of Disease Type

While the state of the art is relatively high with regard to the treatment of specific diseases with a specific agent, it is long underdeveloped with regard to the treatment of soft tissue disease, that is, general treatment, with no specific soft tissue disease combined with a specific drug therefore. In particular, there is no known "treatment" drug, that can treat, "all that ails you". This is why the National Cancer Institute (NCI) has the extensive *in vitro* drug-screening program it does. As discussed by the court in In re Brana, 51 F.3d 1560 (Fed. Cir. 1995), *in vitro* assays are used by NCI (such as the P388 and L1210 lymphocytic leukemia tests at issue therein) to measure the potential antitumor properties of a candidate compound. Brana at 1562-63. If success is shown in this initial screening step, this demonstrates that at least one cancer type (e.g., lymphocytic leukemia) is sensitive thereto, and provides the incentive to select it for further studies to determine its usefulness as a chemotherapeutic agent against other cancer types (lung, breast, colon, etc.) *Id.* at 1567-68. These *in vitro* tests are considered reasonably correlative of success *in vivo*.

Thus, a considerable amount of *in vitro* empirical testing is required, with no *a priori* expectation of success being present, before a candidate for even treating a specific disease, such as, a specific type of soft tissue disease.

2. The breadth of the claims

The claims are very broad and inclusive of "treatment of soft tissue" generally, which includes any soft tissue treatment. Clearly, the methods are only used to treat

diseases, such as carcinomas, sarcomas, myelomas, leukemias, lymphomas and mixed type cancers.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction for ascertaining, *a priori*, which soft tissue diseases can be treated, except those listed in the instant claim 8.

4. The quantity of experimentation necessary

The lack of adequate guidance from the specification or prior art with regard to the actual treatment fails to rebut the presumption of unpredictability present in this art. Applicants fail to provide the guidance and information required to ascertain how the treatment of all soft tissue diseases will be effective without resorting to undue experimentation. Applicant's limited disclosure of the treatment of soft tissue disease is not sufficient to justify claiming the treatment of all soft tissue diseases broadly. Such treatment of such unrelated diseases, having various causes and physiology, would no doubt require undue experimentation.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Larsen et al. (US 2001/0008625A1) in view of Larsen et al. (WO02/05859A2) and further in view of Goldenberg (US 6,083,477).

7. Larsen et al. (US 2001/0008625A1) discloses a receptor binding conjugate, and a kit to prepare the receptor binding conjugate. The receptor binding conjugate comprises an antibody, radionuclide (i.e. ^{227}Th or ^{223}Ra, etc.) and a folate (derivative) (p1, [0001]; p2, [0020],[0025]; claims 19 and 20). Larsen et al. also explicitly discloses that the folate (derivative) may be substituted with another receptor binding molecule, such as oestrogen or testosterone conjugated to the radionuclide-antibody complex for affinity to breast or prostate cancer and that the conjugates of the disclosure are specifically directed to the soft tissue site containing the receptor (p2, [0016]). The method of use of a receptor binding conjugate involves administration via intravenous injection for the imaging of malignant tissue (p2, [0019] and [0025]). The radioimmunoconjugate of the disclosure may be used in combination with other forms of therapy, such as chemotherapy (p2, [0024]). Larsen et al. (US 2001/0008625A1) does not disclose the quantities of ^{227}Th or ^{223}Ra and the treatment with stem cells.

8. Larsen et al. (WO02/05859A2) discloses the method of treating a malignant soft-tissue disease (p1, lines 1-12; p9, lines 24-35) by administering to a mammalian subject (p9, lines 1-11) a ^{227}Th-chelator radiopharmaceutical complexes (p4, lines 35+; p7, lines 19-24). The decay of the ^{227}Th generates in vivo an emissions cascade of α-particles, such as the daughter radionuclide ^{223}Ra that will occur in the target area (p6, lines 33-37; p11, line 12) where ^{223}Ra is the first daughter nuclide in the emissions

cascade of ^{227}Th. The preparation of the ^{227}Th-chelator complex (i.e. DTMP) for administration may be in a pharmacologically acceptable carrier delivered at doses of 10kBq-2MBq/kg bodyweight (p8, lines 30+; p4, lines 17-33; p10, lines 1-16). The reference of Larsen et al. (WO02/05859A2) explicitly states that the ^{227}Th preparation is used for therapy and/or palliation related to malignant diseases affecting bones ***and/or soft tissue***, such as prostate cancer, breast cancer, kidney cancer, etc. (p8, lines 5-20).

9. Also, the method of radiation treatment of a human comprises administering a therapeutically, prophylactically or pain-palliating amount of a bone-targeting complex of an alpha-particle emitting thorium or actinium radionuclide, e.g. for the treatment of calcified tumors, bone tumors, bones, bone surfaces **and soft tissues** (abstract). Therefore the dosages of Larsen et al. (WO02/05859A2) are capable of treating malignant diseases affecting bones ***and/or soft tissue.*** The dosages of the ^{227}Th-chelator complex of the disclosure are taught to reduce myelotoxicity and therefore they would generate the acceptably non-myelotoxic quantity of the daughter radionuclide ^{223}Ra. Therefore the administration of such doses would also cause reduction of the neutrophil cell count to a nadir no less than 10% of the count prior to treatment.

10. Goldenberg (US 6,083,477) discloses a toxin-ligand conjugate that binds to a specific cellular surface marker on a cell and its method of use for tumor therapy (column 1, lines 11-16). The conjugate of the disclosure is a toxin-therapeutic radionuclide complex which effectively localizes to a desired cancer site (column 2, lines 34-38). It is disclosed that doses of antibody and or radioactivity usually require stem

cell rescue and the goal for such is to decrease myelotoxicity generated by an antibody-radionuclide composition (column 1, lines 40-47).

11. At the time of the invention it would have been obvious to one ordinarily skilled in the art to utilize a soft-tissue (i.e. breast tumors) targeting radionuclide complex, such as one taught by Larsen et al. (US 2001/0008625A1) with the doses of Larsen et al. (WO02/05859A2) to reduce the myelotoxicity. The decay of the ^{227}Th generates an emissions cascade of α-particles, such as the daughter radionuclide ^{223}Ra that will occur in the target area where ^{223}Ra is the first daughter nuclide in the emissions cascade of ^{227}Th. The dose of ^{223}Ra is dependent on the decay properties of ^{227}Th radionuclide and since the dosage of Larsen et al. encompasses that of the instant claims, the dose of ^{223}Ra generated in vivo would be equivalent also obviously encompass that of the instant claims. It is advantageous to employ the step of stem cell therapy of Goldenberg (US 6,083,477) since it is known in the art to be used in conjunction with radiotherapy for higher response rates and longer disease-free survival (column 1, lines 40-45). It would be obvious to one skilled in the art to substitute the bone-seeking bisphosphonate DOTA derivative, DTMP (p7, lines 21-24), of Larsen et al. (WO02/05859A2) for a DOTA chelate to eliminate the bone-seeking properties of the radionuclide complex.

12. The method for the treatment of soft tissue disease of the combined disclosures encompass the method for the treatment of soft tissue disease of the instant claims and therefore should have the same properties and be capable of the same functions, such as the T_{bio}, $T_{Th,}$ D_{add}, and D_{Ra}.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1-9,18 and 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,2,4,6,7,9-11,14 and 15 of copending Application No. 10/421,244. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the copending application 10/421,244 are both drawn to the method for treating malignant soft tissue disease in a mammalian subject via administration of a ^{227}Th conjugate comprising a targeting moiety, excluding folate conjugated antibodies. Also the generation of ^{223}Ra via administration of a ^{227}Th conjugate of the instant claims encompasses the generation of 40kBq/kg or less than 150kBq/kg of ^{223}Ra via administration of 36-200kBq/kg or more specifically 75kBq/kg of the ^{227}Th conjugate of

the copending Application No. 10/421,244. The diseases to be treated by the ^{227}Th conjugate (i.e. carcinomas, sarcomas, myelomas, etc.) and the kits of the instant claims are encompassed by those of the copending Application No. 10/421,244.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Melissa Perreira/
Examiner, Art Unit 1618